General

Guideline Title

Management of beta thalassaemia in pregnancy.

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). Management of beta thalassaemia in pregnancy. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2014 Mar. 17 p. (Green-top guideline; no. 66). [56 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

In addition to these evidence-based recommendations, the guideline development group also identifies points of best clinical practice in the original guideline document.

Classification of evidence levels (1++ to 4) and grades of recommendations (A-D) are defined at the end of the "Major Recommendations" field.

Preconception Care

What Is the Optimum Preconceptual Care for Women with Thalassaemia?

D - At each visit with the thalassaemia team, there should be a discussion and documentation of intentions regarding pregnancy. This should include screening for end-organ damage and optimisation of complications prior to embarking on any pregnancy.

Are There Any Interventions Which Are Beneficial at the Preconceptual Stage?

B - Aggressive chelation in the preconception stage can reduce and optimise body iron burden and reduce end-organ damage.

Pancreas

D - Women with established diabetes mellitus should ideally have serum fructosamine concentrations <300 nmol/l for at least 3 months prior to conception. This is equivalent to a glycated haemoglobin (HbA1c) of 43 mmol/mol.

Thyroid

B - Thyroid function should be determined. The woman should be euthyroid prepregnancy.

What Medications Should be Reviewed Preconceptually?

D - Iron chelators should be reviewed and deferasirox and deferiprone ideally discontinued 3 months before conception.

What Is the Importance of Genetic Screening and What Procedure(s) Are Involved for Women with Thalassaemia?

D - If the partner is a carrier of a haemoglobinopathy that may adversely interact with the woman's genotype then genetic counselling should be offered.

D - In vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) with a pre-implantation genetic diagnosis (PGD) should be considered in the presence of haemoglobinopathies in both partners so that a homozygous or compound heterozygous pregnancy can be avoided.

What Is the Importance of Immunisation and Antibiotic Prophylaxis in Women Who Are at Risk of Transfusion-Related Viral Infections or Have Had a Previous Splenectomy?

C - All women who have undergone a splenectomy should take penicillin prophylaxis or equivalent.

C - All women who have undergone a splenectomy should be vaccinated for pneumococcus and *Haemophilus influenzae* type b if this has not been done before.

What Vitamin Supplements Should Be Recommended?

A - Folic acid (5 mg) is recommended preconceptually to all women to prevent neural tube defects.

Antenatal Care

What Is the Optimum Antenatal Management of Iron Chelation Therapy?

Management of Women with Myocardial Iron

C - Women with myocardial iron loading should undergo regular cardiology review with careful monitoring of ejection fraction during the pregnancy as signs of cardiac decompensation are the primary indications for intervention with chelation therapy.

C - Those women at highest risk of cardiac decompensation should commence low-dose subcutaneous desferrioxamine (20 mg/kg/day) on a minimum of 4 to 5 days a week under joint haematology and cardiology guidance from 20 to 24 weeks of gestation.

Intrapartum Care

What Is the Best Intrapartum Management for Women with Thalassaemia Major or Intermedia?

A - Active management of the third stage of labour is recommended to minimise blood loss.

Postpartum Care

What Should Be the Optimum Care Post Delivery?

D - Women with thalassaemia should be considered at high risk for venous thromboembolism.

Definitions:

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Grades of Recommendations

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B - A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; or

Extrapolated evidence from studies rated as 2+

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Beta (β) thalassaemia major and intermedia in pregnancy

Guideline Category

Counseling

Evaluation

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Hematology

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To produce evidence-based guidance on the management of women with beta (β) thalassaemia major and intermedia in pregnancy

Target Population

Women with beta (β) thalassaemia major and intermedia in pregnancy (including preconceptual, antenatal, intrapartum and postnatal management and contraception in both primary and secondary care setting)

Interventions and Practices Considered

Preconception Care

1. Discussion and documentation of intentions regarding pregnancy
    - Screening for end-organ damage
    - Optimisation of complications prior to pregnancy
2. Aggressive chelation
3. Assessment of serum fructosamine concentrations
4. Determination of thyroid function
5. Review of iron chelators
6. Discontinuation of deferasirox and deferiprone
7. Genetic counselling if indicated
8. In vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) with pre-implantation genetic diagnosis (PGD) if indicated
9. Management of women at risk of transfusion-related viral infections or with previous splenectomy
    - Penicillin prophylaxis or equivalent
    - Vaccination for pneumococcus and *Haemophilus influenzae* type b
10. Folic acid supplementation

Antenatal Care

Management of women with myocardial iron loading

- Regular cardiology review and monitoring
- Low-dose subcutaneous desferrioxamine

Intrapartum Care

Active management of the third stage of labour

Postpartum Care

Consideration of high venous thromboembolism risk

Major Outcomes Considered

- Cardiomyopathy in the mother

- Fetal growth restriction
- New endocrinopathies: in particular, diabetes mellitus, hypothyroidism and hypoparathyroidism
- Fertility
- End-organ damage
- Teratogeny
- Breastfeeding
- Haemoglobinopathies and in vitro fertilisation/intracytoplasmic sperm injection
- Pneumococcus and *Haemophilus influenzae* type b
- Neural tube defects
- Myocardial iron loading
- Venous thromboembolism

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This guideline was developed in accordance with standard methodology for producing The Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines. Databases searched included the Cochrane Database of Systematic Reviews, DARE, EMBASE, TRIP, MEDLINE and PubMed. Search terms included: 'beta thalassaemia', 'Cooley's anaemia', 'Mediterranean anaemia', 'hypogonadotrophic hypogonadism', ovulation induction', 'assisted reproduction', 'iron burden', 'serum ferritin', 'penicillin prophylaxis', 'iron chelation', 'fetal growth and measurement' and 'ultrasonography'. The search was limited to humans and the English language and from 1980 to July 2013. Exclusions were alpha thalassaemia or beta thalassaemia minor. There are no systematic reviews in this area and only small numbers of randomised controlled trials looking at particular interventions. The National Guideline Clearinghouse (NGC) was also searched for relevant guidelines and reviews. Where possible, recommendations are based on available evidence. Areas lacking evidence were highlighted and annotated as 'good practice points.'

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classification of Evidence Levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g., case reports, case series

4 Expert opinion

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Reviewing and Grading of Evidence

Once the evidence has been collated for each clinical question it needs to be appraised and reviewed (refer to section 3 in "Development of RCOG Green-top guidelines: producing a clinical practice guideline" for information on the formulation of the clinical questions; see the "Availability of Companion Documents" field). For each question, the study type with least chance of bias should be used. If available, randomised controlled trials (RCTs) of suitable size and quality should be used in preference to observational data. This may vary depending on the outcome being examined.

The level of evidence and the grade of the recommendations used in this guideline originate from the guidance by the Scottish Intercollegiate Guidelines Network (SIGN) Grading Review Group, which incorporates formal assessment of the methodological quality, quantity, consistency, and applicability of the evidence base. The methods used to appraise individual study types are available from the SIGN Web site (www.sign.ac.uk/methodology/checklists.html). An objective appraisal of study quality is essential, but paired reviewing by guideline leads may be impractical because of resource constraints.

Once evidence has been collated and appraised, it can be graded. A judgement on the quality of the evidence will be necessary using the grading system (see the "Rating Scheme for the Strength of the Evidence" field). Where evidence is felt to warrant 'down-grading', for whatever reason, the rationale must be stated. Evidence judged to be of poor quality can be excluded. Any study with a high chance of bias (either 1– or 2–) will be excluded from the guideline and recommendations will not be based on this evidence. This prevents recommendations being based on poor-quality RCTs when higher-quality observational evidence is available.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Development

The development of guidelines involves more than the collation and reviewing of evidence. Even with high-quality data from systematic reviews of randomised controlled trials, a value judgement is needed when comparing one therapy with another. This will therefore introduce the need for consensus.

The Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines are drafted by nominated developers, in contrast to other guideline groups such as the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), who use larger guideline development groups. Equally, in contrast to other guideline groups, the topics chosen for development as Green-top Guidelines are concise enough to allow development by a smaller group of individuals.

In agreeing the precise wording of evidence-based guideline recommendations and in developing consensus-based 'good practice points', the Guidelines Committee will employ an informal consensus approach through group discussion. In line with current methodologies, the entire development process will follow strict guidance and be both transparent and robust. The RCOG acknowledges that formal consensus methods have been described but these require further evaluation in the context of clinical guideline development. It is envisaged that this will not detract

from the rigor of the process but prevent undue delays in development.

Rating Scheme for the Strength of the Recommendations

Grades of Recommendations

A - At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

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Extrapolated evidence from studies rated as 1++ or 1+

C - A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 2++

D - Evidence level 3 or 4; or

Extrapolated evidence from studies rated as 2+

Cost Analysis

A formal cost analysis was not performed and published cost analysis were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Following discussion in the Guidelines Committee (GC), each Green-top guideline is formally peer reviewed. At the same time, the draft guideline is published on the Royal College of Obstetricians and Gynaecologists (RCOG) Web site for further peer discussion before final publication.

All comments will be collated by the RCOG and tabulated for consideration by the guideline leads. Each comment will require discussion. Where comments are rejected then justification will need to be made. Following this review, the document will be updated and the GC will then review the revised draft and the table of comments.

Once the GC signs-off on the guideline, it is submitted to the Clinical Quality Board for approval before final publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate preconceptual, antenatal, intrapartum and postnatal management and contraception in women with beta (β) thalassaemia major and intermedia in pregnancy in both primary and secondary care settings

Potential Harms

- Fertility may be reduced in transfusion-dependent individuals where chelation has been suboptimal and iron overload has occurred resulting in damage to the anterior pituitary.
- Due to lack of safety data, all chelation therapy should be regarded as potentially teratogenic in the first trimester. Desferrioxamine is the only chelation agent with a body of evidence for use in the second and third trimester but should be avoided in the first trimester owing to lack of safety data. The optimisation of iron burden is therefore critical as the ongoing iron accumulation from transfusion in the absence of chelation may expose the pregnant woman to a high risk of new complications related to iron overload, particularly diabetes and cardiomyopathy.
- Women who are transfused regularly or intermittently are at risk of transfusion-transmitted infections. It is therefore important to ascertain infectivity and manage the common transfusion related viral infections appropriately.
- Women with thalassaemia major and myocardial iron loading with T2* of <10 ms are at high risk of cardiac decompensation which may present as increasing breathlessness, paroxysmal nocturnal dyspnoea, orthopnoea, syncope, palpitations or peripheral oedema. Presentation in the first trimester is associated with adverse clinical outcome.

Contraindications

Contraindications

- All bisphosphonates are contraindicated in pregnancy and should ideally be discontinued 3 months prior to conception in accordance with the product safety information sheet
- A reduced ejection fraction is a relative contraindication to pregnancy and the management should be the subject of multidisciplinary discussions involving a cardiologist with experience of cardiac pathology in pregnancy, a maternal medicine specialist, a haematologist and an obstetric anaesthetist

Qualifying Statements

Qualifying Statements

- The Royal College of Obstetricians and Gynaecologists (RCOG) produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available within the appropriate health services. This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.
- These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research might be indicated.

Implementation of the Guideline

Description of Implementation Strategy

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

Mobile Device Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Royal College of Obstetricians and Gynaecologists (RCOG). Management of beta thalassaemia in pregnancy. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2014 Mar. 17 p. (Green-top guideline; no. 66). [56 references]

Adaptation

Not applicable. The guideline was not adapted from another source.

Date Released

2014 Mar

Guideline Developer(s)

Royal College of Obstetricians and Gynaecologists - Medical Specialty Society

Source(s) of Funding

Royal College of Obstetricians and Gynaecologists

Guideline Committee

Guidelines Committee

Composition of Group That Authored the Guideline

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Guideline Committee Lead Reviewers: Dr P Owen FRCOG, Glasgow; Mr M Griffiths FRCOG, Luton

Financial Disclosures/Conflicts of Interest

Conflicts of interest: None declared.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .

Availability of Companion Documents

The following are available:

- Development of RCOG Green-top guidelines: policies and processes. Clinical Governance Advice No 1a. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 6 p. Electronic copies: Available from the Royal College of Obstetricians and Gynaecologists (RCOG) Web site .
- Development of RCOG Green-top guidelines: producing a scope. Clinical Governance Advice No 1b. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 4 p. Electronic copies: Available from the RCOG Web site .
- Development of RCOG Green-top guidelines: producing a clinical practice guideline. Clinical Governance Advice No 1c. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2006 Nov. 13 p. Electronic copies: Available from the RCOG Web site .
- Development of RCOG Green-top guidelines: consensus methods for adaptation of Green-top guidelines. Clinical Governance Advice No 1d. London (UK): Royal College of Obstetricians and Gynaecologists (RCOG); 2010 Feb. 9 p. Electronic copies: Available from the RCOG Web site .

Suggested audit topics can be found in Section 7 of the original guideline document .

In addition, a mobile app for RCOG Green-top guidelines is available from the RCOG website .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 15, 2014. The information was verified by the guideline developer on June 3, 2014.

Copyright Statement

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